Practitioner's Docket No. U 014902-4 *PATENT*

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: MANNE SATYANARAYANA **REDDY**, et al
Application No.: 10/716,200 Group No.: 1614
Filed: NOVEMBER 18, 2003 Examiner:
For: CRYSTALLINE ESOMEPRAZOLE COMPOUNDS AND PROCESS FOR THE PREPARATION THEREOF

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

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Attached please find the certified copy of the foreign application from which priority is claimed for this case:

Country:	INDIA
Application Number:	852/MAS/2002
Filing Date:	FEBRUARY 13, 2002

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Date: March 15, 2004

Signature

JANET I. CORD
(*type or print name of person certifying*)

SIGNATURE OF PRACTITIONER

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S.N. 10/716,200
UO14902-4
Group No.: 1614

THE PATENTS ACT, 1970

It is hereby certified that annexed hereto is a true copy of Application, Complete Specification, Abstract & Drawing of the extract of Patent Application No.852/MAS/2002, dated 18.11.2002 by Dr. Reddy's Laboratories Limited having its registered office at 7-1-27, Ameerpet, Hyderabad 500 016, Andhra Pradesh, India.

.....

.....**In witness thereof**

I have hereunto set my hand

Dated this the 19h day of February 2004

M. S. V

(M.S. VENKATARAMAN)
ASSISTANT CONTROLLER OF PATENTS & DESIGNS

PATENT OFFICE BRANCH
GOVERNMENT OF INDIA
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No.443, Anna Salai, Teynampet,Chennai – 600 018

FORM 1

THE PATENTS ACT, 1970
APPLICATION FOR GRANT OF A PATENT (Section 5(2), 7and Rule 33A)

We, Dr. Reddy's Laboratories Limited, an Indian company having its registered office at 7-1-27, Ameerpet, Hyderabad, Andhra Pradesh, INDIA, 500 016 hereby declare

1. (a) that we are in possession of an invention titled **"Novel crystalline form of Esomeprazole magnesium trihydrate and process for preparation thereof"**
   (b) that the complete specification relating to this invention is filed with this application.
   (c) that there is no lawful ground of objection to the grant of a patent to us.
2. further declare that the inventors for the said invention are **Manne Satyanarayana Reddy, Muppa Kishore Kumar, Koilkonda Purandhar and Lekkala Amarnath Reddy.** All citizens & residents of India belonging to **Dr. Reddy's Laboratories Limited, 7-1-27, Ameerpet, Hyderabad – 500 016, Andhra Pradesh.**
3. that we are the assignee of the true and first inventors
4. that our address for service in India is as follows;

   Dr. Manne Satyanarayana Reddy,
   Vice President-R&D
   Dr. Reddy's Laboratories Limited
   7-1-27, Ameerpet
   Hyderabad, A.P., 500 016
5. following declaration was given by the inventors.
   We, the true and first inventors for this invention declare that the applicant herein is our assignee

Signed)_____

Manne Satyanarayana Reddy,
H.No. 8-3-167/D/16,
Kalyan Nagar,
Near AG Colony,
Erragadda, Hyderabad-500 038.

Signed)_____

Muppa ~~Kishore~~Kumar,
LIG-34, Dharma Reddy Colony,
Phase-I,
KPHB,
Hyderabad-500 072.

Signed) K. Purandhar

Koilkonda Purandhar,
MIG – 129,
Balaji Nagar,
Kukatpally,
Hyderabad – 500 072.

Signed) L.A. Reddy

Lekkala Amarnath Reddy
H.No. 9-101,
Shanthi Nagar,
Dilsuknagar
Hyderabad - 500060.

6. that to the best of our knowledge, information and belief, the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application

7. following are the attachments with the application
   (a) complete specification (---13- pages, in triplicate)
   (b) abstract of the invention (---01- page, in triplicate)
   (c) drawings (---01- pages, in triplicate)
   (d) fee Rs. 5000.00 (five thousand rupees only) in cheque bearing No. "336581" dated October 07th 2002 drawn on HDFC Bank Limited, Lakdikapul, Hyderabad. We request that a patent may be granted to us for the said invention

Dated this 13th day of November 2002.

Signed) M. Satyanarayana Reddy

Dr. Manne Satyanarayana Reddy,
Vice President-R&D
Dr. Reddy's Laboratories Limited.

FORM 2

THE PATENTS ACT, 1970

COMPLETE SPECIFICATION

(SECTION 10)

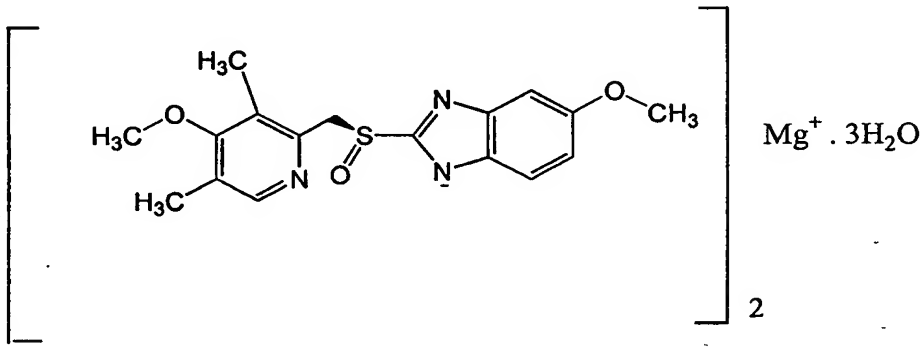
Novel crystalline form of Esomeprazole magnesium trihydrate and process for preparation there of

Dr. Reddy's Laboratories Limited
An Indian Company having its registered office at
7-1-27, Ameerpet
Hyderabad - 500 016, A.P., India

The following specification particularly describes the nature of this invention and the manner in which it is to be performed:

FIELD OF THE INVENTION

The present invention relates to the novel crystalline form of magnesium salt of (-) 5-methoxy-2- [[(4-methoxy-3, 5-dimethyl-2-pyridinyl)-methyl] sulphonyl]-1H-benzimidazole trihydrate (Esomeprazole magnesium trihydrate salt). The present invention also relates to the process for the preparation of novel crystalline form of Esomeprazole magnesium trihydrate salt, which is represented by the following Formula (I).



Formula (I)

BACK GROUND OF INVENTION

Omeprazole, and its therapeutically acceptable alkaline salts are described in EP 5129 and EP 124,495 respectively. Omeprazole and its alkaline salts are effective gastric acid secretion inhibitors, and useful as antiulcer agents. The compounds, being sulfoxides, have an asymmetric center in the sulfur atom i.e., can exist as an optical isomers (enantiomers). It is desirable to obtain compounds with improved pharmacokinetic and metabolic properties, which will give an improved therapeutic profile.

The separation of the enantiomers of Omeprazole in analytical scale is described in J.Chromatography, 532 (1990), 305-19 and in preparative scale in DE 4035455.

DE 4035455 specifically claimed the Esomeprazole and its therapeutically active salts. The patent also disclosed the process for the preparation of enantiomers of Omeprazole by using diastereomeric ether, which is separated and thereafter hydrolyzed in an acidic solution.

USP 6,162,816 disclosed the crystalline forms of Esomeprazole in neutral form namely Form-A and Form-B and characterized by X-ray diffractograms. The process for the preparation of these crystalline forms comprises the recrystallisation of neutral amorphous form of Esomeprazole in different solvents such as ethyl acetate, methylene chloride and toluene to afford the crystalline Form-A and Form-B of Esomeprazole in neutral form.

USP 6,369,085 claimed the novel crystalline form of Esomeprazole magnesium trihydrate salt and characterized by X-ray diffractogram. The said patent also disclosed the process for the preparation of potassium salt of Esomeprazole, characterized by X-ray diffractogram and described the XRD data for dihydrates of Esomeprazole magnesium salt and designated as Form-A and Form-B. The process for the preparation of novel crystalline form of Esomeprazole magnesium trihydrate salt comprises converting the potassium salt of Esomeprazole to corresponding magnesium salt followed by precipitating the resulting magnesium salt by adding acetone and finally by addition of water resulted the Esomeprazole magnesium trihydrate salt.

WO 00/44744 claims the preparation and pharmaceutical composition of potassium salt of Esomeprazole.

The crystalline form of Esomeprazole magnesium trihydrate salt disclosed in USP '085 patent is designated as crystalline Form-I of Esomeprazole magnesium trihydrate for convenience by the present inventors.

The present invention provides a novel crystalline form of Esomeprazole magnesium trihydrate salt. The crystalline form of Esomeprazole magnesium trihydrate salt of the present invention is characterized by X-ray diffractogram and found to be different from the X-ray diffractogram of the prior art forms.

Hence, the novel crystalline form of Esomeprazole magnesium trihydrate salt of the present invention is designated as Form-II of Esomeprazole magnesium trihydrate for convenience and herein after it is referred as crystalline Form-II of Esomeprazole magnesium trihydrate.

The novel crystalline Form-II of Esomeprazole magnesium trihydrate salt of the present invention is more stable than the corresponding magnesium salts disclosed in the prior art and is therefore easier to handle and store. The crystalline Form-II of Esomeprazole magnesium trihydrate salt of the present invention is easier to synthesize in a reproducible manner and thereby easier to handle in full-scale production. The compound of the present invention is also a free flowing and non-solvated crystalline solid, hence may be useful in the preparation of pharmaceutical formulations.

SUMMARY OF THE INVENTION:

The present invention relates to the novel crystalline Form-II of Esomeprazole magnesium trihydrate salt and a process for the preparation there of. The novel crystalline Form-II of Esomeprazole magnesium trihydrate salt of the present invention is characterized by X-ray diffractogram. The process for the preparation of novel crystalline Form-II of Esomeprazole magnesium trihydrate salt comprises the reaction of Esomeprazole with magnesium metal in a mixture of methanol and dichloromethane to result the magnesium salt of Esomeprazole. The resulted salt is successively washed with acetone, recrystallized in methanol and isolated

the solid using mixture of water and acetone to afford the novel crystalline Form-II of Esomeprazole magnesium trihydrate salt.

The process of the present invention is simple, eco-friendly and cost effective, hence it is easier to handle at full-scale production.

BRIEF DESCRIPTION OF ACCOMPANYING DRAWINGS

Fig. 1 is a characteristic X-ray powder diffractogram of the novel crystalline Form-II of Esomeprazole magnesium trihydrate salt obtained in the present invention.

DETAILED DESCRIPTION OF THE INVENTION:

The present invention is directed to the novel crystalline Form-II of Esomeprazole magnesium trihydrate salt and a process for the preparation there of.

The novel crystalline Form-II of the Esomeprazole magnesium trihydrate of the present invention is characterized by the positions and the intensities of the major peaks in the X-ray Powder diffractogram.

The X-ray Powder diffractogram of the compound of the present invention is measured on a Bruker Axs, D8 Advance Powder X-ray Diffractometer with Cu K alpha-1 Radiation source.

The X-ray Powder diffractogram of novel crystalline Form-II of Esomeprazole magnesium trihydrate salt shows well-resolved characteristic peaks, and any other form of magnesium salt of Esomeprazole does not exhibit these peaks.

The relevant X-ray diffractogram of the compound of the present invention is depicted as Figure (1).

The characteristic peaks (in 2-theta values) and their relative intensities (in percentage) are shown in the following Table (1).

Table- (1)

Two-theta (°)	Intensity (%)
4.824	100.0
18.471	81.7
5.552	43
14.16	28.1
12.104	25.3
8.608	22.3
21.089	21.5
7.411	18.8

In further aspect, the present invention provides process for the preparation of novel crystalline Form-II of Esomeprazole magnesium trihydrate salt.

Accordingly, the process for the preparation of novel crystalline Form-II of Esomeprazole magnesium trihydrate salt comprises of;

i) dissolving the magnesium metal in alcoholic solvents comprising of C_1-C_4 straight or branched chain alcohols such as methanol, ethanol, n-propanol, isopropanol, n-butanol or tertiary butanol, preferably methanol accompanied by addition of halo alkane solvent such as dichloromethane;

ii) cooling the mass to a temperature of 5-10^{O}C;

iii) adding the solution of Esomeprazole base in alcohol solvents as described in step (i);

iv) slowly decomposing the reaction mixture by adding water and stirring till the solid separates;

v) filtering the isolated solid obtained in step (iv) by conventional methods;

vi) suspending the wet solid obtained in step (v) in acetone and accompanied by stirring for 1-2 hours at a temperature of 0-5^{O}C;

vii) filtering the solid by conventional methods;

viii) dissolving the solid obtained in step (vii) or an amorphous form of Esomeprazole magnesium in an alcoholic solvents as described in step (i) followed by filtering the solution;

ix) expelling the solvent from the filtrate obtained in step (viii) under reduced pressure;

x) dissolving the solid obtained in step (ix) in a mixture of water and acetone;

xi) cooling the mass to a temperature of –10 to +10^{O}C followed by stirring the mass till solid separates;

xii) filtering the separated solid from step (xi) by conventional methods;

xiii) drying the solid obtained in step (xii) at a temperature of 50-100^{O}C, preferably at 60-70^{O}C to afford the novel crystalline Form-II of Esomeprazole magnesium trihydrate salt.

The amorphous Esomeprazole magnesium salt used in step (viii) of above process has prepared as per the process disclosed in our co-pending Indian Patent application vide no. 638/MAS/2002. The novel crystalline Form-II of Esomeprazole magnesium obtained in the above process is having moisture content in the range of 7.0 to 8.0% by KF method, which indicates the trihydrate salt.

The moisture content of the present inventive substance has measured on Mettler DL-35 instrument using Karl-Fischer reagent.

The novel crystalline form of Esomeprazole magnesium trihydrate salt obtained according to the present invention is substantially free from magnesium salt of (R)-Omeprazole.

The novel crystalline Form-II of Esomeprazole magnesium trihydrate salt obtained in the above process is a non-solvated and free flowing solid.

Hence, the novel crystalline Form-II of Esomeprazole Magnesium trihydrate salt of present invention is well suited for pharmaceutical applications.

The present inventive processes for the preparation of novel crystalline Form-II of Esomeprazole magnesium trihydrate salt is a simple, non-hazardous and well suited for commercial production.

It is noteworthy to mention that the process for the preparation of Esomeprazole magnesium from Omeprazole sodium and further process for the preparation of an amorphous form of Esomeprazole magnesium hydrates are disclosed in our co-pending Indian Patent application number 638/MAS/2002.

The examples that follow will further illustrate the preparation of the compound of the invention, according to different process routes. These examples are not intended to limit the scope of the invention as defined hereinabove or as claimed below.

EXAMPLE-1:

Preparation of novel crystalline Form-II of Esomeprazole magnesium trihydrate salt from crude Esomeprazole:

Magnesium metal (2.08 grams) was suspended in a mixture of methanol (150.00 ml), dichloromethane (5.0 ml) and cooled to a temperature of 5-10^{O}C. Then, to the resulting reaction mixture crude Esomeprazole (50.0 grams)] dissolved in methanol (150.0 ml) was added. Slowly decomposed the resulting reaction mixture by adding water (900 ml) and stirred the reaction mixture till the solid results. Resulting solid mass was filtered, washed with water (300 ml). The wet solid was suspended in acetone (200 ml), stirred the reaction mixture at a temperature of 0-5^{O}C till solid separates. The separated solid was filtered, washed with acetone (50 ml). Further the wet solid was dissolved in methanol (300 ml) and

filtered. Then by expelling the resulting filtrate isolated the white solid. The isolated white solid was recrystallised from a mixture of water (175 ml) and acetone (175 ml). The crystallized solid was dried at a temperature of 60-65°C to afford the novel crystalline Form-II of Esomeprazole magnesium trihydrate salt.

[Weight: 8.5 grams).

EXAMPLE-2:

Preparation of novel crystalline Form-II of Esomeprazole magnesium trihydrate salt from amorphous form of Esomeprazole:

Dissolved the amorphous form of Esomeprazole magnissium salt (25 grams) in methanol (100.00 ml). Filtered the resulting reaction solution through hy-flow bed and washed the bed with methanol (50 ml). Then distilled off the solvent completely from the reaction solution, added water (50 ml) to the resulting residue and stirred the reaction mixture till the solid results. Resulting solid mass was suspended in mixture of water (300 ml) and acetone (300 ml), stirred the reaction mixture at a temperature of 0-5°C till solid separates. The separated solid was filtered, washed with mixture of water (50 ml) and acetone (50 ml). Further the wet solid was suck dried at a temperature of 60-70°C to afford the novel crystalline Form-II of Esomeprazole magnesium trihydrate salt.

[Weight: 14.8 grams)

DETAILED DESCRIPTION OF ACCOMPANYING DRAWINGS:

Fig-1 is characteristic X-ray powder diffraction pattern of novel crystalline Form-II of Esomeprazole magnesium trihydrate salt obtained in the present invention.

Vertical axis: Intensity (CPS); Horizontal axis: 2 Theta (degrees).

The significant 2-theta values obtained are 4.824, 5.552, 7.411, 8.608, 12.104, 14.16, 18.471, and 21.089 degrees two-theta.

We Claim:

1. A novel crystalline Form-II of (-) 5-methoxy-2- [[(4-methoxy-3, 5-dimethyl-2-pyridinyl)-methyl] sulphonyl]-1H-benzimidazole magnesium trihydrate salt (Esomeprazole magnesium trihydrate salt).
2. The novel crystalline Form-II of Esomeprazole magnesium trihydrate salt of claim 1 has X-ray powder diffraction pattern with peaks around 4.824, 5.552, 7.411, 8.608, 12.104, 14.16, 18.471, 21.089 two-theta degrees.
3. The novel crystalline Form-II of Esomeprazole magnesium trihydrate salt of claims 1and 2 having X-ray powder diffraction pattern substantially as depicted in Figure (1).
4. The process for the preparation of novel crystalline Form-II of Esomeprazole magnesium trihydrate salt, which comprises;
    i) dissolving the magnesium metal in alcoholic solvents comprising of C_1-C_4 straight or branched chain alcohols such as methanol, ethanol, n-propanol, isopropanol, n-butanol or tertiary butanol, preferably methanol accompanied by addition of halo alkane solvent such as dichloromethane;
    ii) cooling the mass to a temperature of 5-10^{O}C;
    iii) adding the solution of Esomeprazole base in alcohol solvents as described in step (i);
    iv) slowly decomposing the reaction mixture by adding water and stirring till the solid separates;

v) filtering the isolated solid obtained in step (iv) by conventional methods;

vi) suspending the wet solid obtained in step (v) in acetone and accompanied by stirring for 1-2 hours at a temperature of 0-5^{O}C;

vii) filtering the solid by conventional methods;

viii) dissolving the solid obtained in step (vii) or an amorphous form of Esomeprazole magnesium in an alcoholic solvents as described in step (i) followed by filtering the solution;

ix) expelling the solvent from the filtrate obtained in step (viii) under reduced pressure;

x) dissolving the solid obtained in step (ix)) in a mixture of water and acetone;

xi) cooling the mass to a temperature of –10 to +10^{O}C followed by stirring the mass till solid separates;

xii) filtering the separated solid from step (xi) by conventional methods;

xiii) drying the solid obtained in step (xii) at a temperature of 50-100^{O}C, preferably at 60-70^{O}C to afford the novel crystalline Form-II of Esomeprazole magnesium trihydrate salt.

7. The process according to claim 6 of step (i), where in the said alcohol is methanol.

8. The process according to claim 6 of step (i), where in the said halo alkane solvent is dichloromethane.

9. The processes for the preparation of novel crystalline Form-II of Esomeprazole magnesium trihydrate salt is substantially as herein described and exemplified.

Dated: 13th the day of November 2002 Signed)

Dr. Manne Satyanarayana Reddy,
Vice-President (R&D),
Dr. Reddy's Laboratories Limited.

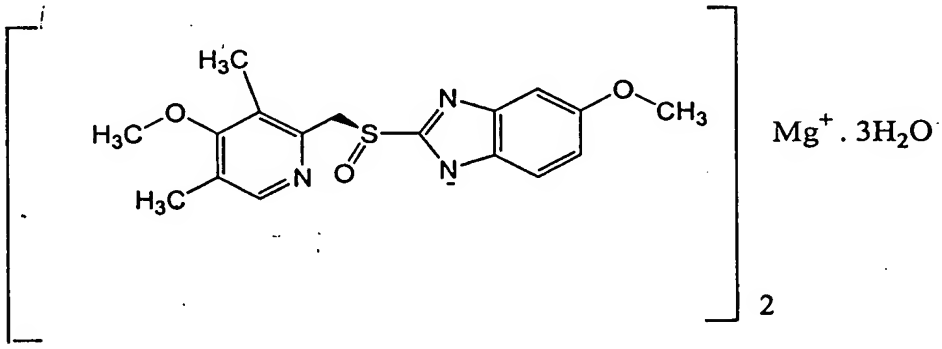
ABSTRACT

Title of the Invention: "Novel Crystalline form of Esomeprazole Magnesium trihydrate and process for preparation thereof"

The present invention relates to the novel crystalline Form-II of Esomeprazole magnesium trihydrate salt and the process for the preparation thereof. Esomeprazole magnesium trihydrate salt is chemically known as (-) 5-methoxy-2- [[(4-methoxy-3, 5-dimethyl-2-pyridinyl)-methyl] sulphinyl]-1H-benzimidazole magnesium trihydrate, which is represented by the Formula (1).

The process for the preparation of novel crystalline Form-II of Esomeprazole magnesium trihydrate salt comprises the reaction of Esomeprazole with magnesium metal in a mixture of methanol and dichloromethane to result the magnesium salt of Esomeprazole. The resulted salt is successively washed with acetone, recrystallized in methanol and isolated the solid using mixture of water and acetone to afford the novel crystalline Form-II of Esomeprazole magnesium trihydrate salt.

The process of the present invention is simple, eco-friendly and cost effective and commercially viable over prior art process.



Formula (1)

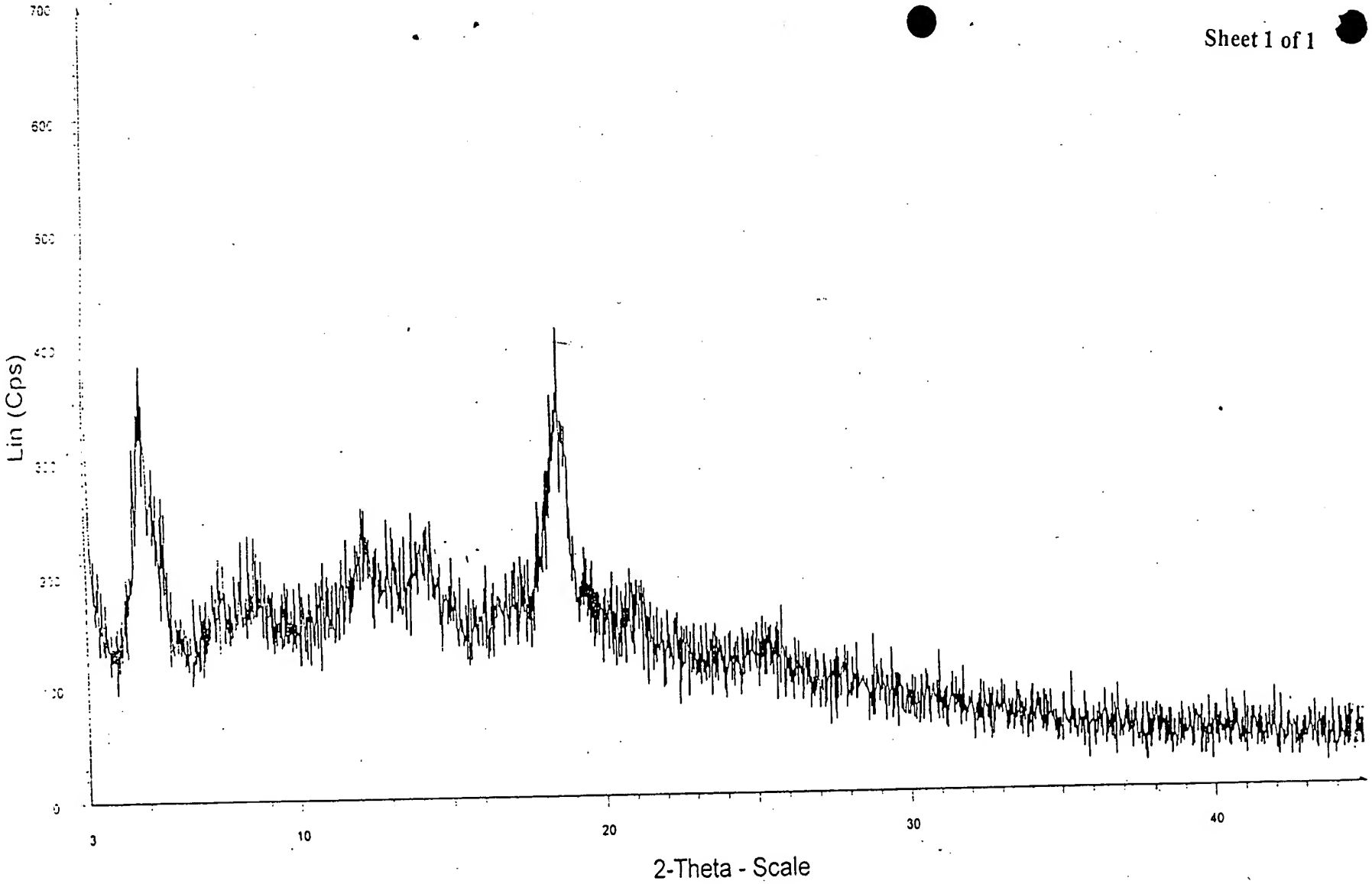


Fig. 1

MANNE SATYANARAYANA REDDY